(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 October 2001 (11.10.2001)

PCT

(10) International Publication Number
WO 01/74343 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/US01/10291

(22) International Filing Date: 30 March 2001 (30.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/193,120 30 March 2000 (30.03.2000) US
09/820,420 29 March 2001 (29.03.2001) US

(71) Applicant: 3M INNOVATIVE PROPERTIES COMPANY [US/US]; 3M Center, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(72) Inventor: SLADE, Herbert B.; Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(74) Agents: HOWARD, MarySusan et al.; Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 01/74343 A2

(54) Title: METHOD FOR THE TREATMENT OF DERMAL LESIONS CAUSED BY ENVENOMATION

(57) Abstract: A method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion is disclosed.

# Method for the Treatment of Dermal Lesi ns Caused by Envenomati n

## Field of the Invention

The present invention relates to methods for treating dermal lesions caused by envenomation. In particular the present invention relates to a method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion. The present invention also provides a method of preventing dermonecrosis caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the envenomation.

## Background of the Invention

Many imidazoquinoline amine, imidazopyridine amine, 6,7-fused cycloalkylimidazopyridine amine, imidazonaphthyridine amine, tetrahydroimidazonaphthyridine amine, oxazolopyridine amine, oxazoloquinoline amine, thiazolopyridine amine, thiazoloquinoline amine and 1,2-bridged imidazoquinoline amine immune response modifiers are known. These compounds are hereinafter sometimes referred to as immune response modifying compounds (IRMs). Such compounds, methods for preparing them, formulations containing them and methods of using them are disclosed in, for example, U.S. Patent Nos. 4,689,338; 5,389,640; 5,268,376; 4,929,624; 5,266,575; 5,352,784; 5,494,916; 5,482,936; 5,395,937; 5,238,944; 5,175,296; 5,693,811; 5,741,908; 5,756,747; 5,939,090; 6,110,929; 4,988,815; 5,376,076; 6,083,505; 6,039,969;

and PCT Publications WO 99/29693, WO 00/40228, WO 00/76505, WO 00/76518 and WO 00/76518.

The IRM compounds have demonstrated antiviral and antitumor activity. The antiviral and antitumor activity is not direct but is believed to result from their ability to stimulate an innate immune response. In cultures of human peripheral blood mononuclear cells, members of this class of compounds have been shown to stimulate the production and release of a variety of cytokines and chemokines including interferon-α, tumor necrosis factor-α, interleukin-1 (IL-1), IL-1 receptor antagonist, IL-6, IL-8, IL-12, monocyte chemotactic protein-1 (MCP-1) and macrophage inflammatory protein (MIP-1α).

In addition to stimulating an innate immune response, the IRM compounds have been found to mediate the acquired immune response. In human peripheral blood mononuclear cell cultures, members of this class of compounds have been shown to induce the production of the T helper type 1 (TH1) cytokine interferon-γ and to inhibit the production of T helper type 2 (TH2) cytokines IL-4 and IL-5.

One of these IRM compounds, known as imiquimod (1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine), has been commercialized in a topical formulation, Aldara™ cream, for the treatment of anogenital warts associated with human papillomavirus. Imiquimod is also being evaluated in clinical trials for use in treating superficial basal cell carcinoma and actinic keratosis.

Another of these IRM compounds, known as resiquimod (4-amino-2-ethoxymethyl-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol), is being evaluated in clinical trials for use in preventing genital herpes recurrences.

There are numerous venomous flora and fauna in the world, some of which possess venom that causes significant medical problems when a human or an animal is exposed to the venom. Envenomation by such a plant or animal can cause both systemic and local reactions. Examples of local reactions include edema, erythema, induration, necrotic ulcers, pain, pruritis, and vesicles. The severity of the reaction is dependent on a variety of factors including the source of the venom (e.g. *Loxosceles* spider, box jellyfish, fire ant), the amount of venom injected, the location of the bite or sting (e.g. arm, thigh), and prior exposure to the venom. A variety of treatments have been used including analgesics, antibiotics, antivenoms, corticosteroids, Dapsone, and hyperbaric oxygen. In those

instances where the initial dermal lesion progresses to dermonecrosis, surgical intervention is often necessary. There is a continuing need for new treatments and in particular for treatments that will prevent dermonecrosis.

## Summary of the Invention

The present invention relates to a method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion.

The present invention also provides a method of preventing dermonecrosis caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the envenomation.

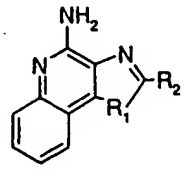
## Detailed Description of the Invention

As used herein the term "envenomation" means injection of a poisonous material (venom) by sting, spine, fang, tooth, or other venom delivery apparatus.

Immune response modifier (IRM) compounds that are useful in practicing the methods of the present invention are selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines. Such compounds and methods for preparing them are disclosed in, for example, U.S. Patent Nos. 4,689,338; 5,389,640; 5,268,376; 4,929,624; 5,266,575; 5,352,784; 5,494,916; 5,482,936; 5,395,937; 5,175,296; 5,693,811; 5,741,908; 5, 756,747; 6,110,929; 4,988,815; 5,376,076; 6,083,505;

6,039,969; and International Publications WO 99/29693; WO 00/76505; WO 00/76518 and WO 00/76518. The entire disclosure of each of these patents and patent applications is incorporated herein by reference.

Preferred IRM compounds for use in the practice of the methods of the invention include compounds of Formula I



I

wherein

$R_1$ is selected from the group consisting of S and $NR_3$,

$R_2$ is selected from the group consisting of hydrogen, straight and branched chain alkyl containing one to six carbon atoms, and alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms; and

$R_3$ is selected from the group consisting of straight and branched chain alkyl containing one to six carbon atoms and straight and branched chain hydroxy alkyl containing one to six carbon atoms; or a pharmaceutically acceptable salt thereof.

Preferred $R_2$ groups include hydrogen, methyl, ethyl, propyl, butyl, and ethoxymethyl.

Preferred $R_3$ groups include 2-methylpropyl and 2-hydroxy-2-methylpropyl.

Particularly preferred IRM compounds include 4-amino-2-ethoxymethyl-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol (resiquimod), 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (imiquimod), 2-methylthiazolo[4,5-*c*]quinolin-4-amine, 2-ethylthiazolo[4,5-*c*]quinolin-4-amine, 2-propylthiazolo[4,5-*c*]quinolin-4-amine and 2-butylthiazolo[4,5-*c*]quinolin-4-amine.

In the method of the invention a therapeutically effective amount of the IRM compound is applied. The term "therapeutically effective amount" means an amount sufficient to induce a therapeutic effect such as the amelioration of symptoms (e.g. pain, erythema diminution of lesions,) or the prevention of dermonecrosis. The specific amount

that will constitute a therapeutically effective amount will vary according to factors readily determined by those skilled in the art including the activity of the particular IRM compound being used, the particular formulation being administered, the duration of the administration and the frequency of the administration. Generally from about 1 μg to about 125 mg, preferably from about 10 μg to about 25 mg, of the IRM compound is applied to the dermal lesion.

Any conventional dosage form suitable for topical application may be used including creams, gels, lotions, ointments, sprays and transdermal patches. Preferred formulations include creams and gels. Suitable formulations are disclosed, for example, in U.S. Patents 5,238,944 and 5,939,090 and International Publication WO 00/40228, the disclosures of which are incorporated by reference herein.

The frequency and duration of administration can vary as needed for amelioration of symptoms and/or prevention of dermonecrosis. Treatment regimens may include administration from twice per day to once per week, preferably two to three times per week, for at least one week, preferably for two to three weeks.

There are many venomous creatures whose bite or sting causes local reactions in humans. Examples of such creatures include, for example, arthropods such as arachnids (e.g., scorpions, spiders) and insects of the order Hymenoptera (e.g., bees, wasps, ants), and marine animals such as jellyfish, stone fish, stingrays, and blue ringed octopus. The venom of some species is known to cause dermal lesions that can progress to dermonecrosis. Examples of such species include *Loxosceles* spiders (*L. reclusa, L. deserta, L. laeta*), hobo spiders (*Tegenaria* spp), yellow sac spiders (*Cheiracanthium* spp.), fire ants (*Solenopsis invicta*), and jellyfish (*Chironex fleckeri, Carybdea alata, Cassiopea andromeda, Aurelia aurita*).

Venoms are frequently complex mixtures of a variety of substances. Substances that have been identified include enzymes e.g. phospholipases, hyaluronidases, cholinesterases; alkaloids e.g. methyl-N-piperidine; proteins e.g. melittin; and peptides. The particular constituents will depend on the source of the venom. When envenomation occurs a number of different types of epithelial and endothelial cells are exposed to the venom. These cells are capable of synthesizing and releasing a wide variety of chemokines and cytokines in response to a variety of stimuli. For example, it has been shown *in vitro* that *Loxosceles deserta* venom induces endothelial and epithelial cells to

secrete both α and β chemokines. The release of chemokines and cytokines triggers additional events such as the attraction of neutrophils to the site of envenomation. While some of the local skin reactions that are manifested as a result of envenomation such as edema and erythema are caused directly by constituents of the venom due to the hemolytic action of various enzymes, it has been hypothesized that dermonecrosis may be due to an immune response.

While not wishing to be bound by theory, it is believed that effects of the IRM compound overwhelm the local physiological effects of the venom. This may occur by modifying the qualitative properties of the local soluble mediators of inflammation such that signaling for neutrophil activation and degranulation is inhibited. In addition, the early aggregation of neutrophils in dermal blood vessels may be diffused by IRM compound induced cytokines by stimulating the migration of neutrophils out of local vasculature and into surrounding tissue. Thus, if activated neutrophils are no longer aggregated in the discrete focal area of the site of envenomation, the amount of central necrosis may be inhibited. In essence, the venom induced "immune dysregulation" may be overcome by the immune stimulation provided by the IRM compound.

## Example

Treatment of *Loxosceles reclusa* envenomation with Imiquimod 5% Cream

### Background

A privatized correctional facility in Texas experienced a cluster of spider bite cases due to *L. reclusa* shortly following the receipt of a shipment of used mattresses from a local county jail. Spiders may have inhabited the mattresses when they were stored for several weeks in a dark shed out behind the facility. Following the first several cases, fumigation with a synthetic pyrethroid (PT 1200, resmethrin) was performed. While this agent is considered effective against *L. reclusa*, the spiders must generally be contacted directly, and unhatched eggs are less susceptible.

The diagnosis of loxoscelism in these cases was made by exclusion. No spiders were recovered despite the use of glue traps, although in one case, a "brown spider" dropped from the ceiling of a shower onto the breast of a female patient, who brushed the spider away after sustaining a bite. The following aspects of these cases favor a diagnosis

of *L. reclusa* envenomation: the spider is endemic to the area; the bites occurred mostly at night and were characterized by lack of immediate pain. Blanching and cyanosis slowly developed at the central core, with spreading erythema and progression to dermonecrosis. Other insects are known to inflict bites with similar clinical findings but can be excluded on the grounds that they are not found in Texas (various tarantulas, Australian funnel-web spiders (*Atrax spp.*), "hobo spiders" (*Tegeneria spp.*); they form characteristic webs not found in the facility (yellow sac spiders (*Chiracanthium spp.*), black-and-yellow orb weavers (*Argiope spp.*); or they bite during the day ("jumping spider" (*Phidippus audax*)). *Phidippus* species are very aggressive and bite commonly, but they inflict only slightly painful bites resulting in erythematous papules or small urticarial wheals. The only alternative suspect is *Latrodectus mactans* ("Southern black widow"). This spider is shy in behavior, similar to *L. reclusa*, and bites often go unnoticed until a red papule progresses to a larger halo or target lesion up to 2 cm in diameter. Unlike the *L. reclusa* bite however, skin manifestations are minimal. Victims are more likely to experience muscle spasms and cramping within hours of envenomation, together with weakness of the legs and tightness of the chest. These clinical findings were absent in the cases reported here.

Methods

Patients were seen in the facility clinic on the day they complained of a painful lesion. Most patients related a history of discovering the lesion upon awakening in the morning. The treatment of the first 12 consecutive cases, occurring over a 5 month period, consisted of a single intramuscular dose of ceftriaxone 1 gm and oral dicloxicillin 500 mg bid x 10 days, plus either topical triamcinolone 0.1% applied bid, topical papain-urea-chlorophyllin copper complex sodium debriding-healing ointment (Panafil™) applied daily, or daily topical becaplermin (rh-PDGF-BB) 0.01% gel (Regranex™). Where necessary and appropriate, patients were transported to the local University Medical Center for surgical debridement of necrotic lesions.

A consecutive series of 7 bites on 5 patients were treated with imiquimod 5% cream (available under the tradename ALDARA from 3M Pharmaceuticals, St. Paul, MN, USA) applied by the clinic staff, three times per week (typically Monday, Wednesday and Friday) for two weeks. Sufficient cream was used to cover the area of erythema, rubbing

the cream gently until it "vanished" as per labeled instructions. In addition, a single intramuscular dose of ceftriaxone 1 gm was given together with oral dicloxicillin, 500 mg bid for 10 days. Patients were re-examined by a physician at 7, 14 and 28 days following initiation of therapy.

Results

The first 12 patients, managed using conventional therapy, presented with tender to painful lesions consisting of a central core of induration and blanching, surrounded by 3-8 cm of erythema. Among these, 7 progressed to tissue necrosis within 1 week after the bite, all of whom were referred for surgical debridement. One patient developed a healing contracture of the forearm which necessitated surgical release. Healing occurred by secondary intention over several months following the bites.

Seven consecutive bites occurring in 5 patients were treated with imiquimod. These cases are summarized in the Table below. Presenting signs and symptoms were consistent with those recorded for patients treated by conventional means. Tenderness or pain, with erythema, characteristic blanching and firm induration were present in every case. In one case (L.S.), punctuate marks were noted at the center of the indurated area. Pain relief was reported by all patients within 1-2 days following the first dose of imiquimod. Marked improvement in both induration and erythema was noted by day 7, with full resolution in all but one case by day 14. In patient Y.C., erythema was noted to be cleared at the day 7 visit but developed again by day 14. The reappearance of erythema is presumed to be secondary to imiquimod

Patients C.R. and L.S. each sustained two bites. In the case of L.S., the first bite was resolved 9 days after it occurred. The second bite occurred 16 days after the first bite and resolved completely, with treatment, by the 5th day. The difference in clinical course may have been due to differences in the age of the spider, the sex of the spider (females inject greater volumes of venom), or an acquired immunity following the first bite. Necrosis did not develop in any of the imiquimod treated cases. No residual scarring or pigmentation changes were noted at the day 28 follow-up visit.

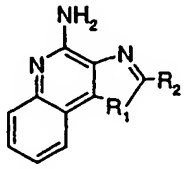
The probability of observing 0 out of 7 consecutive cases with no necrosis, given the underlying historical rate of 7/12 (0.583), is quite low based on a binomial probability distribution ($p=0.002$) or a Chi-square analysis ($p=0.01$).

| Summary of Cases | | | | |
|---|---|---|---|---|
| Patient/Age/Sex | Bite Location | Presentation | 7 Day Follow-up | 14 Day Follow-up |
| R.M/ 39y/ M | Right calf | 1.5 cm induration<br>9 cm erythema<br>Painful | 0.5 cm induration<br>No erythema<br>No pain or tenderness | Completely healed |
| R.H/ 45y/ M | Right calf | 1.3 cm induration<br>10 cm erythema<br>Very painful | 1.25 cm firm induration<br>5 cm induration<br>Non-tender | Completely healed |
| L.S./ 28y/ F | Right thigh | 1.5 cm induration<br>7.5 x 11 cm erythema<br>Tender | 2.5 cm central core<br>No erythema<br>No pain or tenderness | Completely healed |
| L.S./ 28y/ F | Left buttock | 1.0 cm induration<br>Erythema<br>Painful | Completely healed | |
| C.R./ 35y/ F | Left thigh | 1.0 cm central core<br>6.0 cm erythema<br>Painful | 0.5 cm central core<br>2.0 cm erythema | Completely healed |
| C.R./ 35y/ F | Right breast | 1.2 cm central core<br>3.0 cm erythema<br>Painful | 1.0 cm central core<br>No erythema | Completely healed |
| Y.C./ 35y/ F | Right calf | 1.8 cm central core<br>1.2 cm erythema<br>Painful | 0.75 cm ulcer<br>No erythema<br>Decreased pain | Ulcer healed<br>Erythema present<br>(Erythema resolved by d28) |

WHAT IS CLAIMED IS:

1. A method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion.

2. The method of Claim 1 wherein the immune response modifier compound is a compound of Formula I



I

wherein

$R_1$ is selected from the group consisting of S and $NR_3$,

$R_2$ is selected from the group consisting of hydrogen, straight and branched chain alkyl containing one to six carbon atoms, and alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms; and

$R_3$ is selected from the group consisting of straight and branched chain alkyl containing one to six carbon atoms and straight or branched chain hydroxy alkyl containing one to six carbon atoms; or a pharmaceutically acceptable salt thereof.

3. The method of Claim 2 wherein $R_1$ is $NR_3$.

4. The method of Claim 2 wherein $R_1$ is S.

5. The method of Claim 2 wherein $R_2$ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, and ethoxymethyl.

6. The method of Claim 2 wherein $R_3$ is selected from the group consisting of 2-methylpropyl and 2-hydroxy-2-methylpropyl.

7. The method of Claim 2 wherein the IRM compound is selected from the group consisting of 4-amino-2-ethoxymethyl-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 2-methylthiazolo[4,5-*c*]quinolin-4-amine, 2-ethylthiazolo[4,5-*c*]quinolin-4-amine, 2-propylthiazolo[4,5-*c*]quinolin-4-amine and 2-butylthiazolo[4,5-*c*]quinolin-4-amine.

8. The method of Claim 1 wherein the immune response modifier compound is applied via a cream or a gel.

9. The method of Claim 1 wherein the source of the envenomation is an arthopod.

10. The method Claim 9 wherein the arthopod is a spider.

11. The method of Claim 9 wherein the arthodpod is an insect of the order Hymenoptera.

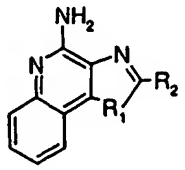
12. The method of Claim 1 wherein the source of envenomation is a marine animal.

13. The method of Claim 12 wherein the marine animal is a jellyfish.

14. A method of preventing dermonecrosis caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline

amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the envenomation.

15. The method of Claim 14 wherein the immune response modifier compound is a compound of Formula I



I

wherein

$R_1$ is selected from the group consisting of S and $NR_3$,

$R_2$ is selected from the group consisting of hydrogen, straight and branched chain alkyl containing one to six carbon atoms, and alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms; and

$R_3$ is selected from the group consisting of straight and branched chain alkyl containing one to six carbon atoms and straight or branched chain hydroxy alkyl containing one to six carbon atoms; or a pharmaceutically acceptable salt thereof.

16. The method of Claim 15 wherein $R_1$ is $NR_3$.

17. The method of Claim 15 wherein $R_1$ is S.

18. The method of Claim 15 wherein $R_2$ is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, and ethoxymethyl.

19. The method of Claim 15 wherein $R_3$ is selected from the group consisting of 2-methylpropyl and 2-hydroxy-2-methylpropyl.

20. The method of Claim 15 wherein the IRM compound is selected from the group consisting of 4-amino-2-ethoxymethyl-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-

ethanol, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, 2-methylthiazolo[4,5-*c*]quinolin-4-amine, 2-ethylthiazolo[4,5-*c*]quinolin-4-amine, 2-propylthiazolo[4,5-*c*]quinolin-4-amine and 2-butylthiazolo[4,5-*c*]quinolin-4-amine.

21. The method of Claim 14 wherein the immune response modifier compound is applied via a cream or a gel.

22. The method of Claim 14 wherein the source of the envenomation is an arthopod.

23. The method Claim 22 wherein the arthopod is a spider.

24. The method of Claim 22 wherein the arthodpod is an insect of the order Hymenoptera.

25. The method of Claim 14 wherein the source of envenomation is a marine animal.

26. The method of Claim 25 wherein the marine animal is a jellyfish.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 October 2001 (11.10.2001)

PCT

(10) International Publication Number
WO 01/74343 A3

(51) International Patent Classification[7]: A61K 31/4745, 31/429

(21) International Application Number: PCT/US01/10291

(22) International Filing Date: 30 March 2001 (30.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/193,120 30 March 2000 (30.03.2000) US
09/820,420 29 March 2001 (29.03.2001) US

(71) Applicant: 3M INNOVATIVE PROPERTIES COMPANY [US/US]; 3M Center, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(72) Inventor: SLADE, Herbert B.; Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(74) Agents: HOWARD, MarySusan et al.; Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*

(88) Date of publication of the international search report:
7 February 2002

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 01/74343 A3

(54) Title: METHOD FOR THE TREATMENT OF DERMAL LESIONS CAUSED BY ENVENOMATION

(57) Abstract: A method of treating dermal lesions caused by envenomation comprising applying a therapeutically effective amount of an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines to the site of the lesion is disclosed.

# INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 01/10291

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4745 A61K31/429

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 93 20847 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 28 October 1993 (1993-10-28) cited in the application the whole document | 2-7, 15-20 |
| A | WO 00 06577 A (3M INNOVATIVE PROPERTIES CO.) 10 February 2000 (2000-02-10) cited in the application the whole document | 2-7, 15-20 |
| A | US 5 389 640 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 14 February 1995 (1995-02-14) cited in the application the whole document | 2-7, 15-20 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 19 October 2001 | 31/10/2001 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Economou, D |

1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,8-14,21-26

Present claims 1,8-14,21-26 relate to an extremely large number of possible compounds/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds/methods disclosed in claims 2-7 and 15-20.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

ormation on patent family members

Inter . .onal Application No
PCT/US 01/10291

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9320847 A | 28-10-1993 | AT 142110 T | 15-09-1996 |
| | | AU 674313 B2 | 19-12-1996 |
| | | AU 4048093 A | 18-11-1993 |
| | | DE 69304521 D1 | 10-10-1996 |
| | | DE 69304521 T2 | 20-02-1997 |
| | | DK 636031 T3 | 24-02-1997 |
| | | EP 0636031 A1 | 01-02-1995 |
| | | ES 2092306 T3 | 16-11-1996 |
| | | HK 1007962 A1 | 30-04-1999 |
| | | HU 69993 A2 | 28-09-1995 |
| | | HU 9500752 A3 | 28-11-1995 |
| | | IL 105325 A | 14-11-1996 |
| | | JP 7505883 T | 29-06-1995 |
| | | KR 263804 B1 | 16-08-2000 |
| | | MX 9302199 A1 | 31-08-1994 |
| | | NO 943920 A | 14-10-1994 |
| | | NZ 252020 A | 21-12-1995 |
| | | NZ 280098 A | 26-06-1998 |
| | | WO 9320847 A1 | 28-10-1993 |
| | | US 6083505 A | 04-07-2000 |
| | | ZA 9302627 A | 14-10-1994 |
| WO 0006577 A | 10-02-2000 | US 6110929 A | 29-08-2000 |
| | | AU 5133199 A | 21-02-2000 |
| | | EP 1100802 A1 | 23-05-2001 |
| | | NO 20010497 A | 27-03-2001 |
| | | WO 0006577 A1 | 10-02-2000 |
| US 5389640 A | 14-02-1995 | US 5977366 A | 02-11-1999 |
| | | US 5605899 A | 25-02-1997 |
| | | US 5741909 A | 21-04-1998 |
| | | AT 179711 T | 15-05-1999 |
| | | AU 658621 B2 | 27-04-1995 |
| | | AU 1566992 A | 06-10-1992 |
| | | AU 673309 B2 | 31-10-1996 |
| | | AU 2715795 A | 21-09-1995 |
| | | CA 2104782 A1 | 02-09-1992 |
| | | CZ 9301788 A3 | 18-10-1995 |
| | | DE 69229114 D1 | 10-06-1999 |
| | | DE 69229114 T2 | 04-11-1999 |
| | | DK 582581 T3 | 08-11-1999 |
| | | EP 0582581 A1 | 16-02-1994 |
| | | EP 0872478 A2 | 21-10-1998 |
| | | ES 2131070 T3 | 16-07-1999 |
| | | HU 67026 A2 | 30-01-1995 |
| | | HU 211242 B3 | 28-11-1995 |
| | | IE 920605 A1 | 09-09-1992 |
| | | IL 101110 A | 08-12-1995 |
| | | IL 114570 A | 31-10-1996 |
| | | JP 2955019 B2 | 04-10-1999 |
| | | JP 6504789 T | 02-06-1994 |
| | | KR 235389 B1 | 15-12-1999 |
| | | NO 933069 A | 01-11-1993 |
| | | NZ 241784 A | 27-06-1995 |
| | | SG 46492 A1 | 20-02-1998 |
| | | SG 70625 A1 | 22-02-2000 |
| | | WO 9215582 A1 | 17-09-1992 |
| | | ZA 9201540 A | 25-11-1992 |